December 7, 1951

Dr. A. D. Hershey
Dept. Genetics
Carnegie Institution
Cold Spring Harbor, L.I.,N.Y.

Dear Al:

Are you acquainted at all with the Vi-phage-typing diagnosis of S. typhi? Having read only the rather unsatisfactory papers of Craigie and Yen (Can. P. H. J., 29: 448 and 484) I never had a very clear picture about it. But a student from Reed's laboratory at Queens College, Kingston, Ont., is spending a year here and gave a seminar about it that raised some very interesting features.

As best as I could tell, the phages for Vi group II are all obtained from a pure line phage. This phage has a high e.o.p. only for the Vi-type on which it was propagated, a much lower eop (10^{-4} ?) for any other type. The residual plaques found on heterologous indicators always give rise to an adapted stock which now has a high eop for its host, and a low eop on all the others.

At first sight one can argue simply for a complex of host-range mutations selected from the phage stocks. The host-range patterns are, however, quite unique, since activity (at high eop) for all the other alternative hosts is lost upon adaptation to any given one. There are a dozen or more distinct Vi types.

Your work on phenotypic mixing is very relevant to the adaptation, in my opinion. It seems to me possible that there is a directed host adaptation which is <u>not</u> a mutation, in the same sense as the modification of the phenotypes in the output of T2-T4 mixed infections. The residual plaques are not mutants, but those phage particles (with a random, non-inherited character) which accidentally succeed in initiating infection on a heterologous host. Having done so, the output phenotype is directed by the host in which they have grown. The decisive question as to whether this is a mutation or not is whether a particular specificity is inherited in a heterologous host. On the mutation hypothesis, selection prevents an answer. I do think, however, that the problem is soluble, either by statistical studies on the numbers of "mutant" phages in different cultures (a la Luria and Delbruck) especially if differential absorption can be used to alter the proportions of different types, or by the indirect selection (by replica plating) approach.

We are not going to do these experiments, but would be interested to hear what you think of the idea. The Canadian student conceivably might want to, but almost certainly could not do as good a job as someone with more experience and insight (namely A.D.H.)

Yours sincerely,

Joshua Lederberg